Amendment to the Drawings

Please replace the 16 original drawings sheets with the 27 drawings sheets submitted herewith, which includes 11 replacement sheets and 16 new sheets.

Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Catastrophic heart rhythm disorders are among the leading causes of death in the United States. The most dangerous of these arrhythmias is ventricular fibrillation, a disturbance in which disordered wave propagation causes a fatal disruption of the synchronous contraction of the ventricle. Although the exact mechanism for fibrillation is still being debated, one theory proposes that fibrillation is a state of spatiotemporal chaos consisting of the perpetual nucleation and disintegration of spiral waves, in association with a period doubling bifurcation of local electrical properties. Nucleation of the initiating spiral wave pair is caused by local conduction block (wave break) secondary to spatial heterogeneity of refractoriness in the ventricle. Until recently, spatial heterogeneity was thought to result solely from regional variations of intrinsic cellular electrical properties or from stimulation at more than one spatial location. However, it is now appreciated that purely dynamical heterogeneity can be sufficient to cause conduction block during single-site stimulation in both homogeneous one-dimensional models of canine heart tissue and in rapidly paced canine Purkinje fibres. A similar mechanism has been shown to precipitate conduction block and spiral break-up in models of homogeneous two-dimensional tissue.

The period doubling bifurcation implicated in the transition to conduction block is manifest as alternans, a beat-to-beat long–short alternation in the duration of the cardiac action potential. Previous investigators have hypothesized that alternans can be accounted for by a simple uni-dimensional return map called the action potential duration restitution function. This hypothesis assumes the duration D of an action potential depends only on its preceding rest interval I through some function $f(I)$ that is measured experimentally. If the D restitution function has a slope ≥ 1, then a period doubling bifurcation occurs for some value of the stimulus period T, where $T = D + I$. The velocity V at which an action potential propagates can also be described by a restitution function, where $V = c(I)$.

It has also been shown previously that the combination of a steeply sloped action potential duration ("APD") restitution function and a monotonically increasing conduction velocity ("CV") restitution function is sufficient to produce dynamical conduction block during sustained pacing at a short cycle length. This observation may provide a generic mechanism for wave break and the onset of ventricular tachycardia and fibrillation.

However, it is unlikely that the conditions used to demonstrate this phenomenon experimentally apply to the clinical situation, where the induction of ventricular tachyarrhythmias typically is associated with the interruption of normal cardiac rhythm by only a few premature beats. A single premature beat is sufficient to cause spatial heterogeneity in the form of discordant alternans, but the conditions required for the development of conduction block in this setting have not been studied extensively.

Other studies, building on earlier theoretical work by Krinsky, Winfree and colleagues (Krinsky et al, "Votices with Linear Cores in Mathematical Models of Excitable Media," *Physica A* 188:55-60 (1992) and Winfree, A., "Evolving Perspectives During 12 Years of Electrical Turbulence," *Chaos* 8:1-20 (1998)) and experiments by Allessie (Allessie et al., "Circus Movement in Rabbit Atrial Muscle as a Mechanism of Tachycardia. III. The 'Leading Circle' Concept: a New Model of Circus Movement in Cardiac Tissue Without the Involvement of an Anatomical Obstacle," *Circ Res* 41:9-18 (1977)), have suggested that spiral wave re-entry could be the 'engine' that drives ventricular fibrillation ("VF"). Although there is substantial evidence that spiral wave re-entry contributes significantly to the induction and maintenance of VF, the exact mechanisms by which spiral waves sustain VF is currently being debated.

The present invention is directed towards correctly identifying the mechanisms (or more likely, mechanisms) by which spiral waves cause VF and the development of pharmacological approaches to VF treatment and prevention.

The November 17, 2009, personal interview between Examiner Porter, Examiner Layno, inventor Robert Gilmour, Michael Goldman, and Megan Thisse is gratefully acknowledged. Applicants note that the interview was a personal interview at the U.S. Patent and Trademark Office rather than a telephonic interview as set forth in the Interview Summary, mailed on November 19, 2009. The substance of that interview is summarized below.

Pursuant to 37 CFR § 1.125(b), applicants submit the enclosed substitute specification, excluding claims. In compliance with 37 CFR § 1.121(b)(3), applicants respectfully request that the enclosed substitute specification replace the originally-filed specification. In compliance with 37 CFR § 1.125(c), attached hereto are a clean version of the substitute specification (Appendix 1) and a marked-up version showing all changes relative to the originally-filed specification (Appendix 2). In particular, paragraph [0002] is amended to state that the government has certain rights in the invention. Paragraphs [0023], [0025], [0026], [0052], [0053], [0055], [0057], [0060] – [0063], [0073], [0077], [0079],

[0080], and [0082] are amended to change the reference to stimuli from S1-S5 to S'1-S'5 as requested by Examiner Porter to reduce confusion with other commonly known variables. Paragraph [0066] is amended to recite "...shifting the curve from Figure *10A* down by subtracting 70 ms from $f(M_{n+1}, I_n)$." (emphasis added). Applicants submit that this corrects a typographical error that would be readily apparent to one of skill in the art, as demonstrated by the recognition of that typographical error in the outstanding office action at paragraph 7. Applicants submit that the substitute specification contains no new matter.

By this amendment, 27 sheets of drawings have been submitted to replace the original 16 sheets of drawings. Figures 4B, 5, 6, 7, 8B, 8C, 9B, 9C, 9D, 10B, 10C, 10D, 11, and 12 have been amended to reflect the changes in nomenclature of stimulus from S to S', as discussed above.

By the above amendments, claims 1-31 are cancelled and claims 32, 33, 35, 36, and 38 are amended. Written descriptive support for these amendments is found in the present application, as filed, at paragraphs [0005], [0021], [0023], [0026], [0057], [0058], and [0059]. No new matter is added. Claims 32, 35, and 38 are pending and being examined. Claims 33, 34, 36, and 37 are withdrawn from consideration.

The objection to the specification under 35 U.S.C. § 112 (1st para.) for lack of clarity is respectfully traversed in view of the above amendments and the following remarks.

It is the position of the PTO that it is unclear how conclusions are drawn in paragraph [0026] with respect to S4 and S5 from Figure 7, and it is unclear what the exact values for the minimum time intervals at points S2 and S3 are. As discussed during the Interview, Figure 7 does not show values for S4 and S5, but those values are predicted using the formula of amended claim 32. It was also pointed out that minimum time intervals at points S2 and S3 that allow conduction down the fiber are determined experimentally, and the S2-S3 protocol is well known in the art, as evidenced by Koller et al., "Dynamic Restitution of Action Potential Duration During Electrical Alternans and Ventricular Fibrillation," *Am. J. Physiol. Heart Circ. Physiol.* 275:1635-1642 (1998) (Appendix 3).

It is also the position of the PTO that paragraph [0066] lacks clarity. As discussed during the Interview, paragraph [0066] recites that "shifting the curve shown in Figure 10D by subtracting 70ms from $f(M_{n+1}, I_n)$ produced roughly the same number of blocks (941651) as in Figure 10D." First, the typographical error that appears in this section (as pointed out in the outstanding office action at paragraph 7) is corrected, as noted above. Further, it is Applicants' position that one of skill in the art could understand from reading the instant specification that 70 ms is a significant shift.

Accordingly, in view of these amendments and remarks, the objection to the specification under 35 U.S.C. § 112 (1st para.) for lack of clarity is improper and should be withdrawn.

The objection to the drawings under 37 C.F.R. §1.121(d) is respectfully traversed in view of the accompanying replacement set of drawings.

The rejection of claims 32, 35, and 38 under 35 U.S.C. § 101 for being directed to non-statutory subject matter is respectfully traversed in view of the above amendments. Thus, this rejection is improper and should be withdrawn.

The rejection of claims 32, 35, and 38 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed in view of the above amendments. Thus, this rejection is improper and should be withdrawn.

The rejection of claims 32, 35, and 38 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments. Thus, this rejection is improper and should be withdrawn.

The rejection of claims 32 and 35 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent Application Publication No. 2005/0059897 to Snell et al. ("Snell") is respectfully traversed.

Snell teaches methods and devices for analyzing intracardiac electrocardiograms using statistical analysis, ensemble averaging, and/or ensemble average, which are suitable for use with atrial and/or ventricular pacing therapies.

Snell fails to teach a method of identifying treatment therapies as therapeutic strategies for preventing ventricular tachycardia from developing into ventricular fibrillation. In particular, Snell does not teach the steps of detecting ventricular tachycardia in a subject, monitoring intervals between electrical stimuli in the heart of the subject, and determining if an initial 3 stimuli in groups of 4 stimuli from said monitoring in the heart correspond to rest interval values (*I*) predicted to lead to ventricular fibrillation as defined by the equation recited in amended claim 32.

For these reasons, the rejection of claims 32 and 35 under 35 U.S.C. § 103(a) for obviousness over Snell is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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